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Award Number: W81XWH-10-1-0780

TITLE: Oculomotor reflexes as a test of visual dysfunctions in cognitively impaired observers

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REPORT DATE: September 2013

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE September 2013		2. REPORT TYPE Final		3. DATES COVERED 30 September 2010 – 29 September 2013	
4. TITLE AND SUBTITLE Oculomotor reflexes as a test of visual dysfunctions in cognitively impaired observers				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-10-1-0780	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) YuryPetrov,Ph.D. E-Mail: yury@ski.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Northeastern University Boston, MA 02115				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT We successfully developed and implemented a battery of visual tests designed to diagnose various visual dysfunctions by means of recording and objectively analyzing passive oculomotor reflexes. All hardware and software components of the data acquisition and analysis pipeline were finalized and tested in realistic experimental conditions on normal observers and several observers with visual dysfunctions. Observers received no instructions from us regarding their task except for attending to the screen. This passive viewing regime imitated experimental conditions for testing cognitively impaired patients. The project results indicate that the adopted paradigm has sufficient statistical power to successfully diagnose various visual dysfunctions, which validates the proposed approach.					
15. SUBJECT TERMS eye-tracking, oculomotor reflexes, visual dysfunctions,					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	21	19b. TELEPHONE NUMBER (include area code)

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Introduction

The project aimed to develop a battery of tests to diagnose visual dysfunctions in cognitively impaired observers based on their oculomotor reflexes. The oculomotor reflexes provide a simple and robust method to study vision in passive/immature/impaired observers. For example, oculomotor reflexes are widely used to study vision in infants and in marketing research. The proposed method is versatile, applies to a wide range of visual mechanisms, and can provide both qualitative (yes/no) and quantitative (degree) estimates of the visual loss. The project embodies a full research and development cycle, from establishing the most effective stimuli for various kinds of visual dysfunctions to the design of a computerized testing kit suitable for use by non-specialists. After a short training course, the kit could be used at army bases and local hospitals to make a quick initial diagnosis.

Body

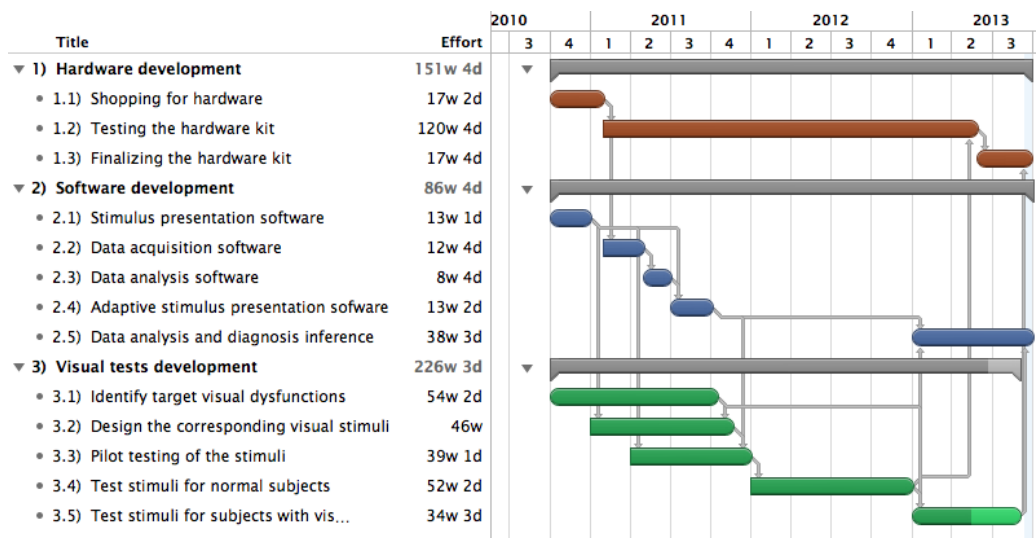


Figure 1: Gantt chart for the project.

As specified in the Statement of Work, the main goal of the first 12 months of the project was to design effective stimuli allowing the oculomotor reflexes to be used as diagnostic tools for various visual dysfunctions. The three reflexes proposed for this project (optokinetic reflex, pupillary reflex, orienting reflex) form a complementary set. For example, our preliminary data demonstrated that optokinetic reflex in response to drifting gratings is an effective tool for testing various low-level visual mechanisms, such as visual acuity, contrast sensitivity, color, and depth sensitivities. On the other hand, orienting and pupillary responses to salient stimuli can be used to test higher-order visual functions, such as shape perception, face recognition, visual memory, etc. Even if the subject's eye movements are impaired by the injury, the pupillary reflex alone can be used as a qualitative diagnostic tool for both the low-level and the high-level visual functions.

The main goal of the second 12-months period of the project was to make the tools developed in the first aim available to non-specialists. To this end, a computerized testing kit based on an automatic eye-event registration algorithm was developed. The kit is used to present visual stimuli, collect eye-position and pupil-size data and search the data for relevant ocular reflexes evoked in a real-time automated regime. Based on the analysis, an adaptive algorithm chooses/adjusts the test stimuli for the next round of stimulation until a certain reliability level is achieved and the battery of tests is exhausted.

The main goal of the third and final 12-month period of the project was to test a large cohort of normal observers on the developed stimuli and hardware kit in order to accumulate the normative distribution of performance scores. It was also planned to test a large number of patients with visual dysfunctions. Then, using the normative distribution, the test results for the observers with visual dysfunctions in the form of percent correct performance scores could be translated to the probabilities of various visual dysfunctions, hence validating the proposed diagnostic method.

Figure 1 shows a Gantt chart indicating project tasks and their current state of completion. The following project goals were met: we selected and purchased all the necessary hardware for the project, identified common visual dysfunctions, designed stimuli testing for these dysfunctions, and developed the necessary software to present the stimuli, capture the eye-tracking data, and analyse it for the relevant eye-events. This completed the hardware and software kit building phase. Ocular reflexes evoked by the developed stimuli were captured for 120 normal observers. The data were used to calculate normative distributions and predictive power of each of the tested stimuli. These tasks are described in detail in the following sections.

Hardware development

Different models of eye-trackers were investigated in the first quarter of year 1. The goal was to find the model best suited for the project, i.e., portable, and well suited for experimental work with cognitively impaired subjects. Other search parameters included programming interface capabilities, ease and speed with which hardware customizations could be made, and the overall cost. After investigating several eye-tracker models being used on Northeastern University campus and visiting local manufacturers of eye-tracking equipment we purchased two video-based eye trackers from ISCAN Inc. (based locally in Woburn, MA): one in remote and one in head-mounted configuration (Figure 2). This allowed us to test both eye-tracking

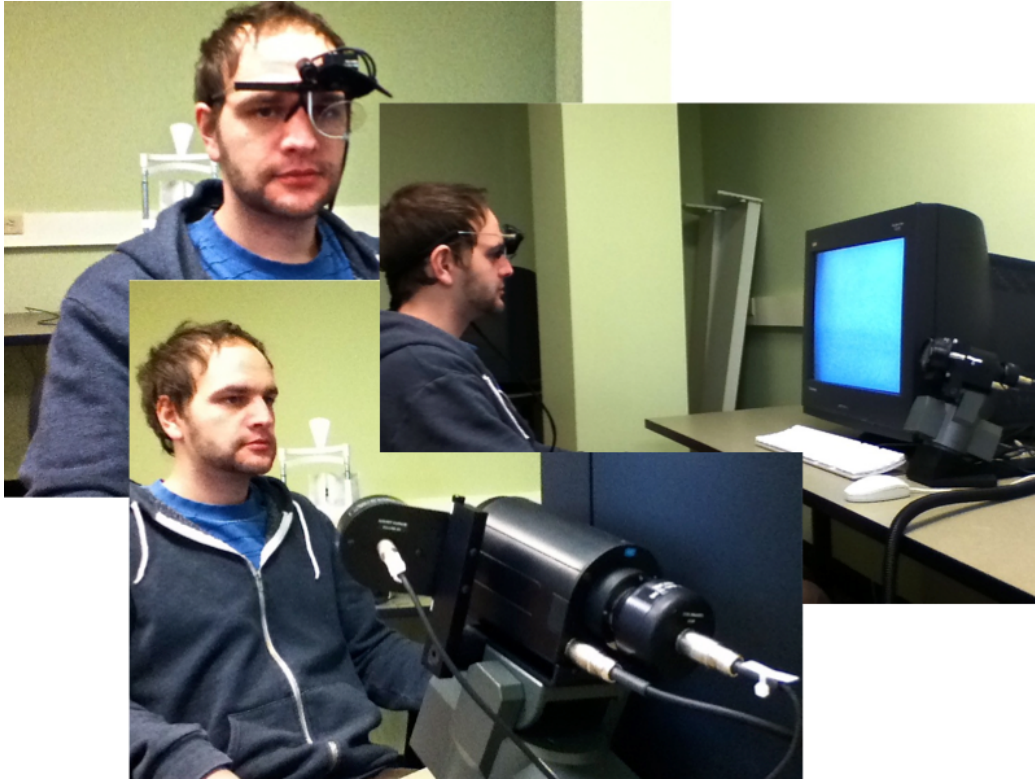


Figure 2: Two ISCAN Inc. eye-trackers used for the project. The head-mounted unit is mounted on a safety goggles frame. The remote unit is positioned next to the monitor.

modes and to find the one best suitable for this project.

The eye-tracking units came with a laptop and desktop computers. The laptop computer is more portable, but currently can only be used for 120 Hz eye-tracker sampling rate. The desktop can be used for 240 Hz sampling rate, but is less portable. Accumulated data indicates that 120 Hz is adequate for our purposes, but we are leaving the 240 Hz option open, because the higher sampling speed might be necessary for noisier data (subjects with droopy eyelids, thick glasses, uncontrolled head-movements, etc.).

The complete hardware kit (the head-mounted configuration) finalized by the end of year 1 is shown in Figure 3. To ensure maximum performance two computers (laptops) are used. One computer is dedicated to controlling the eye-tracker. Stimulus generation, presentation, data collection, and data analysis are carried out by another computer. The two computers communicate via serial connection. Eye images are sampled at 120 Hz by the ISCAN Inc. eye-tracker. Video components of the eye-tracker include miniature



Figure 3: The complete hardware kit. The data-collection laptop is on the left, the video-presentation and data analysis laptop is on the right. The eye-tracker is in the center, its electronics (MiniLab) is in the back, the head-mounted eye cameras and IR mirror attached to a safety-goggle frame are in the front. The Keyspan serial-USB adapter connecting the eye-tracker to the data-analysis laptop can be seen in the center.

eye- and scene-cameras, infrared (IR) illuminator LED, and an IR mirror all mounted on a safety-goggles frame positioned on a subject's head. The electronic components (MiniLab) include hardware-implemented algorithms for segmenting the pupil image from the eye image and calculating the pupil's position and size. MiniLab also includes hardware for serial data output. The eye-tracker is controlled from the laptop shown on the left. ISCAN software installed on the laptop provides an intuitive graphical user interface (GUI) allowing to control the eye-tracker in a simple fashion. In particular, it is used to optimize the camera settings for various lighting conditions and, if required, for glasses or contact-lenses worn by the subject. The laptop shown on the right is used for visual stimulation and online analysis of the eye-tracking data. Visual stimuli are presented either on the laptop screen or on a dedicated monitor (not shown). The eye-tracking data is received in real-time regime from the MiniLab electronics via a 6 ft. serial cable. The data is received on a USB port of the laptop via a Keyspan serial-USB adapter (model USA-19HS).

The head-mounted version of the eye-tracker can be mounted on a baseball cap if the safety-goggles frame is not tolerated by the subject. If neither version of the head-mounted device can be safely worn by the subject the remote (desktop mounted) eye-tracker with automatic head tracking can be used. The remote eye-tracker can also be used for detecting dysfunctions in

binocular convergence for all subjects, because it allows to track both eyes simultaneously (stimuli are not currently implemented). The hardware kit was tested both in PI's laboratory and in field conditions. In particular, the kit was transported to Brown University, where a subject with recent TBI-related visual dysfunctions was tested in typical office settings. The kit weighing about 20 pounds can be transported in a medium-sized backpack. It takes approximately 10 minutes to assemble the kit, to power up the laptop computers and to get them ready for the test.

Visual tests development

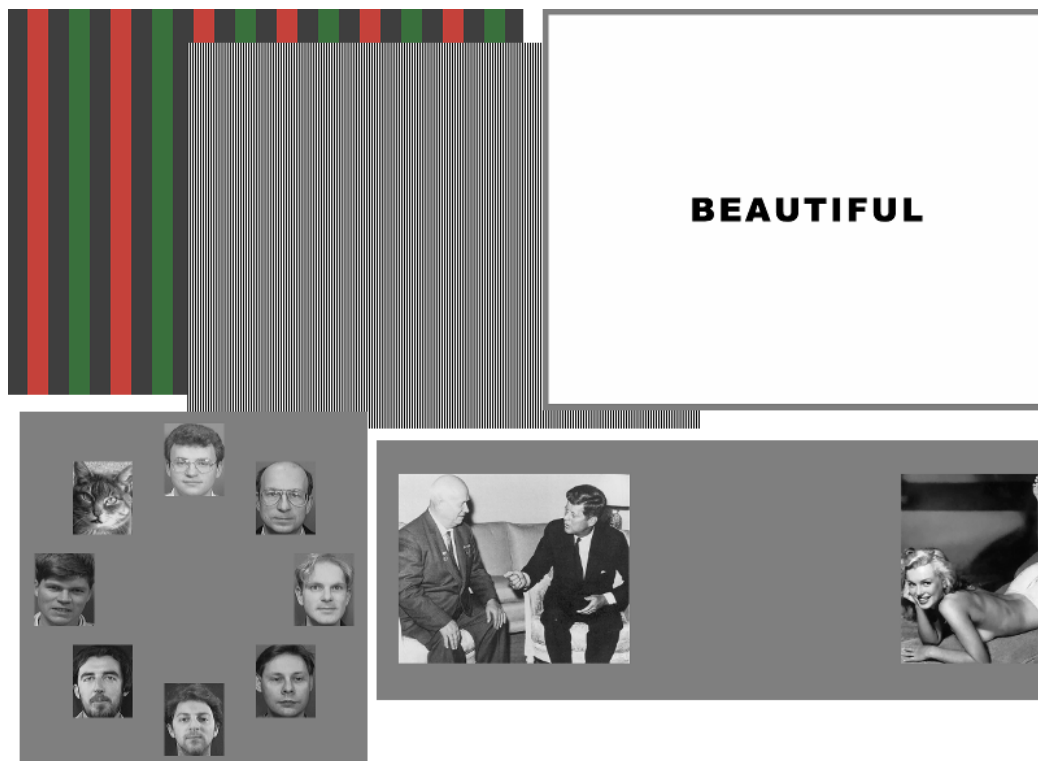


Figure 4: Examples of visual stimuli used for the study. Drifting gratings (top left) were used to evoke optokinetic reflex, neutral and mildly offensive words (top right) were used to evoke pupillary response, images of odd-ball and mildly arousing female figures were used to evoke orienting reflex (saccades) and pupillary response.

In the second, third, and fourth quarters of year 1 we collected and analyzed pilot data for normal observers. Pilot stimuli included various drifting

gratings and odd-ball images of faces, bodies, and words. Figure 4 shows some examples. The images were obtained from freely available research databases. Typical pilot session lasted 6 minutes during which 30 - 40 visual stimuli were shown. Subjects were viewing stimuli on a 21" LCD monitor from a distance of 60 - 80 cm. The head-mounted version of the eye-tracker was used for all subjects, eye-movements were sampled at 120 Hz. At this stage the data were collected off-line: recorded on a hard drive during the experimental run and analyzed after its completion. The pilot data was used to optimize the visual stimuli and to design/test eye-event filters as described below. A fragment of the pilot data for one subject is shown in Figure 5.

Eventually, the stimuli were used to evoke reflex eye-movements in 120 normal observers. We received clearances from the Northeastern University IRB and MEDCOM USAMRMC for work with human subjects in March 2011. PI and his graduate students were used as subjects prior to this date. We used inexperienced observers naive to the purpose of the test: observers only knew that they were taking part in an eye-tracking experiment. The only instructions received from the experimenter were to attend to the screen. Such experimental conditions were chosen to simulate testing cognitively impaired observers.

Reflex	Stimulus	Functions
Visual Nystagmus	luminance grating equiluminant grating contrast gratings at 3 spatial scales semi-coherently drifting dots	low-level motion color vision visual acuity high-level motion
Orienting Reflex	contour / texture boundary odd image (animal among males) seminude female vs. 'boring' male	low-level object processing high-level object processing high-level object processing
Pupillary reflex	mild curse in a random word stream odd word within a sentence	mid-level reading high-level reading

Table 1: Oculomotor reflexes, the stimuli used to evoke the reflexes, and the corresponding tested visual functions.

The pilot stimuli developed and tested during year 1 were improved at the end of year 2 to produce more robust eye events suitable for automated detection. The finalized battery of visual stimuli along with the associated ocular reflexes, and the corresponding tested visual functions are described in Table 1. In particular, we developed a new stimulus for visual nystagmus to

test visual motion processing in the presence of incoherent motion noise. The drifting equiluminant color grating stimulus used for testing color deficiencies was redesigned to make the evoked visual nystagmus much more robust. Because the absolute gaze is not measured in our paradigm (this would require a gaze calibration, involving significant cooperation of the subject) the orienting reflex has to be measured with respect to an undefined gaze position at the time of the stimulus onset. To attract the gaze to the center of the screen a disk contrast-reversing for 500 msec was added at the center of the screen 1000 msec before the stimulus onset. In addition, the odd-ball image and contour/boundary stimuli used to evoke the orienting reflex were simplified to make the evoked eye movements less dependent on the gaze position at the time of the stimulus onset. To this end, the odd image or the contour/boundary was positioned in one of the 4 quadrants on the screen (compared to 8 such positions used in pilot stimuli). The test was considered passed if the subject's gaze stayed in the 'interesting' quadrant significantly longer than in the remaining quadrants. The odd-word stimulus originally designed to test the ability to read and comprehend isolated words was extended to include complete sentences, where the ability to understand the logical structure of a written text is also tested.

Software development

Once the eye-tracking units arrived in January 2011, we started software development for visual stimulus presentation, eye-tracking data readout, and the data analysis.

Visual stimulus presentation and data import

A software library for adaptive visual stimulus generation, presentation, and analysis (C++ and OpenGL based) was developed. This library is used to create visual stimuli and to collect real-time data from the eye-tracker. The data is received from the eye-tracker computer via serial connection. The library incorporates a graphical user interface, which allows to easily observe eye events and to vary the stimulus parameters.

Eye-event filters

Using the collected pilot data we designed software filters for automatic detection of the relevant eye events in real time. Altogether, 4 types of filters

were developed: blinks, saccades, optokinetic reflex (nystagmus), and pupillary response (contraction/dilation). The filters are based on measuring and thresholding eye-movement velocities and pupil area changes. The filters were designed to be used with real-time data: they are fast and they do not require large amounts of data to work. About one second of data is sufficient to detect saccades and pupillary reflex, and several seconds of data – to detect optokinetic reflex (which, typically, lasts for 3 – 5 seconds at a time).

In the pilot stage (year 1) the filters were validated using human-parsed fragments of the pilot data. The collected eye-tracking data were searched and parsed into different types of relevant eye events, such as blinks, visual nystagmus, saccades, and pupil dilations. Half of the data were used to design the software filters, the other half were used for filter testing. Filter performance for the high-amplitude eye events relevant to our project was close to 100% dropping below 90% for very noisy data only. Identifying saccades was the task most affected by noise. Noisy data can result from poorly adjusted eye-tracker parameters. Such adjustments are particularly important when subjects are wearing glasses, have droopy eyelids, or narrow eyes. Altogether, the filters performance was found adequate for the purposes of our project. The four eye-event filters (blinks, saccades, nystagmus, and pupillary reflex) prototyped in MATLAB in the course of year 1 were implemented in C++ in year 2. This allowed us to increase the filters speed and to unite stimulus generation and data analysis into a feedback loop within the same application running on the data-analysis laptop. The filters are based on measuring and thresholding eye-movement velocities and pupil area changes. From the start the filters were designed to be used with real-time data: they are fast and do not require large amounts of data. Less than a second of data is sufficient to detect saccades and pupillary reflex, and several seconds of data – to detect visual nystagmus which, typically, lasts for 3 – 5 seconds at a time. In year 2 we thoroughly redesigned the nystagmus and pupil dilation filters to make their output more robust to subjective variations. To this end we developed a new algorithm, where the eye-tracking data is analyzed at different time scales and then the resulting filter outputs are integrated across the scales. We also completely redesigned the filter used to measure the orienting reflex (eye-movement and the following viewing of an interesting object). Instead of relying on the direction of the first saccade we used a different approach based on measuring how long the subject’s gaze stayed within the area of interest compared to the rest of the scene. This measure proved to be more robust to the effect of the (somewhat unpredictable) gaze position at the beginning of the trial.

Figure 5 illustrates the filters performance. Raw eye-tracking data (a single trial in each case) are shown by the black symbols, the outputs of the

corresponding filters are marked in red. Panel *a* illustrates a filter response to a significantly longer viewing of an odd (animal face) image shown in the bottom-right quadrant. Panel *b* illustrates a similar paradigm, where a semi-nude female image shown in the left half of the screen was viewed longer than a 'boring' male image in the right half. The filter response, again, indicates a significantly longer viewing of the 'interesting' image. Panel *c* illustrates a robust visual nystagmus arising in response to the stimulus where a coherent drift of some dots is masked by incoherent random movements of the remaining dots. Panel *d* illustrates a pupillary dilation in response to a mild curse word suddenly appearing within a sequence of 'ordinary' words presented on the screen.

The visual stimuli and the respective filters were optimized in year 3 to make the filter performance maximally independent of subjective variations in the eye-tracking data. This is most crucial while detecting the pupillary response to a surprising stimulus (e.g., a curse word), where the latency, amplitude, and duration of the pupil dilation were found to vary significantly from trial to trial and also among subjects.

Testing normal observers

Once the Northeastern University IRB and MEDCOM USAMRMC approvals for work with human subjects were renewed in October 2011 we collected and analyzed data for twenty five normal observers and two observers with possible visual dysfunctions. 120 more observers were tested in the course of year 3. The large number of observers is necessary to accumulate enough statistics to estimate the distribution of test scores (percent correct) among normal observers. This distribution was later used to convert the test scores to the probability of visual dysfunctions.

Northeastern University undergraduate students of both sexes 18 - 25 years of age with normal or corrected vision were recruited as normal subjects. The subjects were inexperienced observers naive to the purpose of the test. The only instructions received from the experimenter were to attend to the screen. Before the test all subjects were questioned on any visual dysfunctions they might have had and only those subjects reporting normal vision were used. The subjects and experimental conditions were meant to simulate testing cognitively impaired soldiers. Experimental sessions lasted 6 minutes during which 80 visual stimuli were shown. Subjects were viewing stimuli on a 21" LCD monitor from a distance of 60 - 80 cm. The head-mounted version of the eye-tracker was used for all subjects, pupil (left eye) position on the camera's CCD was sampled at 120 Hz. The data were collected and analyzed by the developed software filters in real time and then

saved on the hard drive of the data-analysis laptop. A fragment of the data and the accompanying automatic eye-event segmentation for one subject are shown in Figure 5.

Testing observers with visual dysfunctions

Due to the termination of the PI’s contract with Northeastern University in July 2013, we were unable to perform measurements on a large cohort of patients with visual/cognitive dysfunctions, which were planned for the terminal stages of the project. However, in the course of the project we were able to identify and test four subjects with recent history of brain injury or visual dysfunctions. Given the small number of observers with visual dysfunctions tested, it is impossible to draw definite conclusions about the effectiveness of our approach to testing visual dysfunctions using passive oculomotor reflexes. However, the results presented below make a case for cautious optimism.

Subject S1 (a female, 37 years old) had a severe traumatic brain injury 8 months prior to the test. As a result, her control of eye movements was initially disrupted to the extent that for several months she could not read at all, could not do her work or travel. At the time of the test she described her visual functions as almost normal. Superficially, her eye movements also appeared normal. However, compared to normal subjects, S1 showed very low scores in the coherent dot motion test: her performance fell below that for 92% of normal subjects. This is even more surprising given that S1, being a vision scientist herself, was exposed to similar stimuli more frequently than the tested normal observers. Such low probability score strongly suggests that S1’s complex motion processing was not restored to its normal.

Subject S2 (a male, 70 years old) had a foveal retinal detachment in both eyes. A year prior to the test he was operated. The first operation was unsuccessful in the right eye, but after the second operation he reported his vision to be mostly restored in both eyes. He was wearing his normal vision correction during the experiment. Subject S2 showed very low scores for contrast-defined nystagmus: for the stimulus requiring the highest acuity his performance was lower than that for 91% of normal subjects. In addition, his performance in the color nystagmus task lower than for 82% of normal subjects. These results indicate that S2’s foveal vision was relatively poor, lacking in color sensitivity and acuity.

Subjects S3 (a male, 21 years old) and S4 (a male, 20 years old) were picked from the general pool of normal observers based on their own verbal report of suspected color vision deficiencies. Both subjects took an online color-deficiency test (<http://www.biyee.net/color-science/color-vision-test>) imme-

diately prior to the experiment. The test confirmed that the subjects had significant green blindness: their percentages of correct responses on the deuteranopia test were well below the corresponding threshold. Both subjects reported that they could see the drifting grating most of the time, however, their performance in this test was lower than for 90% of normal subjects. This indicates that the red and green colors used for our color-defined grating were perceived by these subjects not equiluminant, apparently, due to their green cone deficiencies.

Data Analysis

In the second half of year 3 we analyzed ocular responses of 120 normal subjects recorded in the previous phases of the project. The large number of normal observers was necessary to accumulate enough statistics to estimate the distribution of normal test scores (percent correct). The calculated normative distributions are plotted in the left panel of Figure 6. Blue bars represent the probability distribution of evoking and detecting an ocular reflex for a particular stimulus as specified by the title of each subplot. Red bars represent the same for a 'Null' response, which simulates the breakdown of normal responses for patients with severe visual dysfunctions. The Null distributions were calculated by using eye movements evoked by all the stimuli dissimilar to the tested one, i.e., irrelevant to the tested stimulus. For example, for a condition in which visual nystagmus was tested all the stimuli except the ones with drifting gratings were used to calculate the Null distribution. The resulting predictive power of the classification between a normal and a dysfunctional observer is proportional to the extent the two distributions (blue and red) are separated. The receiver operating characteristic (ROC) analysis was performed to measure the power, and the resulting ROC curves are shown in the right panel. The area under each ROC curve gives the probability of a normal subject performing better than a severely dysfunctional subject in the particular task. The corresponding probability is shown by the number within each subplot. The results allowed to identify those tests which have high predictive power and those test which do not. For example, the orienting reflex to an animal face among human faces appears to be very robust, whereas the orienting reflex to an upside-down human face among normal-side-up human faces is so weak that it has almost zero predictive power.

Taking 75% probability as the threshold test power we see that most of the stimuli used in the tests can be used for testing observers in a passive way, i.e. without the observers being aware of any task. Thus, all nystagmus stimuli except for the coherent drifting dots are acceptable. The latter one

is close to the threshold (71%), and can also be used once the dot coherence is increased above the currently used 25%. These stimuli can be used to test visual acuity (coarse, medium, fine gratings), color deficits (color gratings) and complex motion processing deficits (coherent dots drift). The two of the orienting reflex stimuli passed the power threshold: simple target (disk) orienting, and orienting to complex objects (animal face among human faces). These stimuli can be used to test dysfunctions at early and late stages of visual processing. Finally, performance for the stimuli used for testing visual processing of text (65% and 62%) did not pass the 75% threshold. Careful investigation of raw eye-tracking data showed that the low performance resulted from spurious pupil dilations irrelevant to the surprise words used in the test. Most likely, these dilations were caused by subjects shifting their gaze back and forth between the stimulus text shown in black on bright white field and the surrounding screen areas colored in neutral gray. These eye movements could cause abrupt changes in average illumination of the fovea, which would result in the observed spurious pupil dilations and contractions. We surmise that the spurious pupil reactions can be lessened or completely avoided by using text nearly equiluminant to the neutral gray background, e.g., shown in blue matched in luminance to the background. We find it likely that stimulus modifications along these lines could raise the performance above the threshold level.

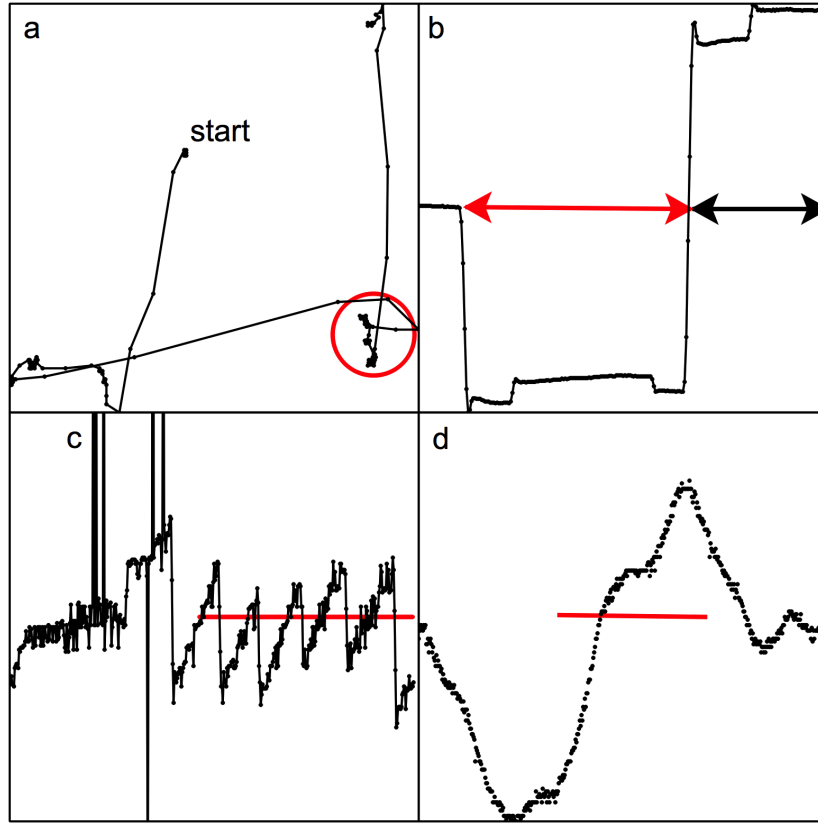


Figure 5: Eye tracking data and the corresponding filter outputs. Time from the stimulus onset is plotted along the x-axis in panels b – d. (a) An animal face was shown in the bottom-right quadrant, 3 human male faces were shown in the remaining quadrants. Gaze point readings (x and y coordinates on the camera's CCD) are marked by the black dots. Only 3 images were explored by the subject's gaze. The red circle indicates a significantly longer viewing of the bottom-right image detected by the filter. (b) a semi-nude Marilyn Monroe image was shown in the left half of the screen, a male figure in a suit was shown in the right half. Gaze horizontal position is plotted along the y-axis. A significantly longer viewing of the left image detected by the filter is indicated by the red arrow. (c) For the first quarter of the trial randomly placed dots were moving in a 'random walk' fashion, afterwards 25% of the dots were also drifting to the right. Gaze horizontal position is plotted along the y-axis. The red bar indicates a visual nystagmus event detected by the filter. (d) A mild curse word was displayed on a white background at the beginning of the trial. Pupil area is plotted along the y-axis. The red bar indicates pupil dilation detected by the filter. The pupil contraction at the beginning of the trial resulted from the response to the white background of the text.

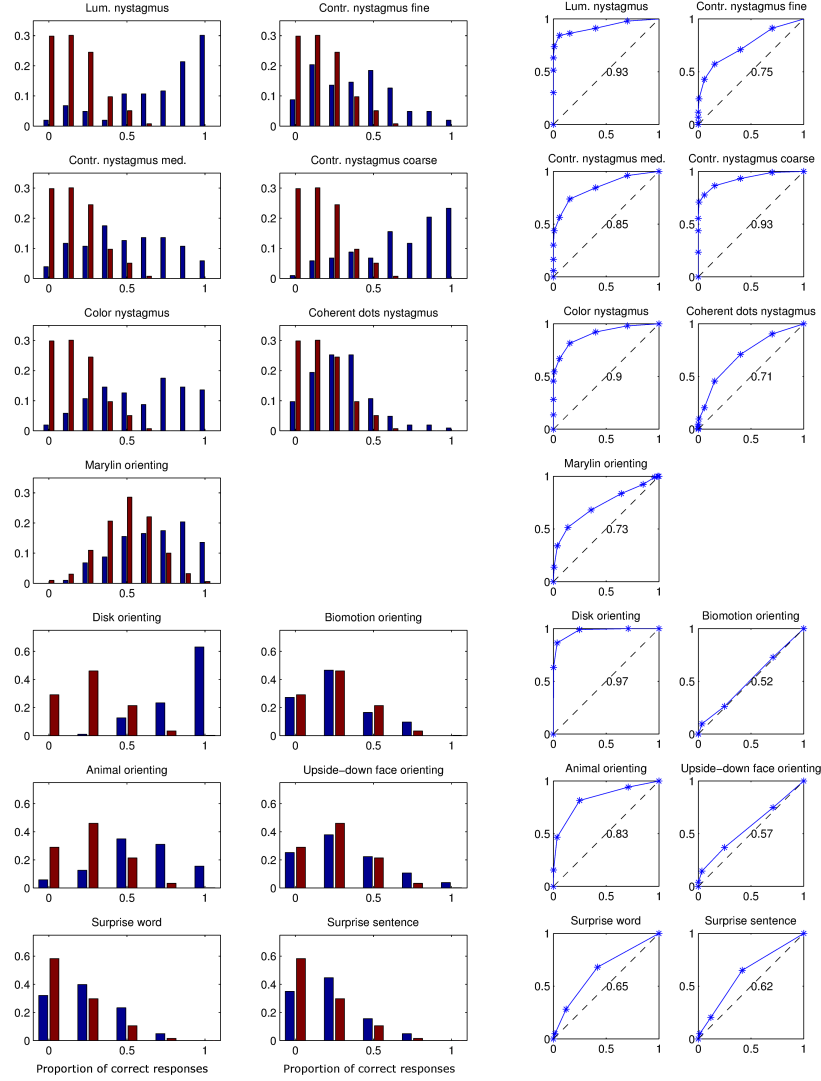


Figure 6: Left panel: Normative response distributions based on results for 120 observers. Blue bars show distributions for normal observers, red bars show Null distributions modeled on task-irrelevant eye movements of the observers. Right panel: receiver operating characteristic (ROC) analysis of the predictive power for each task. Number within each subplot indicates the probability of correctly detecting a dysfunction for the tested reflex assuming a complete breakdown of the reflex for each task.

Key Research Accomplishments

- We identified and purchased two eye-tracker models, head-mounted and desktop-mounted, which can be used to carry out robust eye-tracking for patients with cognitive disabilities.
- A software library for adaptive visual stimulus generation, presentation, and data acquisition was developed.
- Visual stimuli were designed and tested on normal observers naive to the purpose of the test. No specific instructions were given to simulate experiments with cognitively impaired observers. The collected data was used to optimize the visual stimulation and to design software filters which allow automatic detection of relevant reflex eye movements in real time.
- Real-time data exchange between the eye-tracker and the data-analysis computer was implemented, tested, and optimized. This finalized the hardware kit development.
- Eye-event filters for automatic ocular reflex detection were designed, implemented in C++, and incorporated into the software running on the visual stimulation and data analysis laptop. The real-time processing of the data allowed to make the testing adaptive.
- The complete kit was tested on 120 normal observers naive to the purpose of the test and four observers with possible visual dysfunctions either congenital or resulting from recent TBI/eye injuries.
- Using the data, normative performance distributions were calculated for the tested stimuli.
- When compared with normal subjects the observers with possible visual dysfunctions showed significantly lower performance ($< 90\%$ of the norm), which appear to be in agreement with their symptoms and clinical histories.

Reportable Outcomes

There were no reportable outcomes yet. We are in the process of preparing a publication based on the results of the study. In particular, it will report the new result: unlike a salient object stimulus, e.g., an animal face among human faces, a salient motion stimulus, biological motion vs. scrambled motion, does not attract attention (does not pop-out). We also are preparing to file a patent describing the current approach to passively assessing visual functions using ocular reflexes.

Conclusions

We successfully developed and implemented a battery of visual tests designed to diagnose various visual dysfunctions by means of recording and objectively analyzing passive oculomotor reflexes. All hardware and software components of the data acquisition and analysis pipeline were finalized and tested in realistic experimental conditions on normal observers and several observers with visual dysfunctions. Observers received no instructions from us regarding their task except for attending to the screen. This passive viewing regime imitated experimental conditions for testing cognitively impaired patients. The project results indicate that the adopted paradigm has sufficient statistical power to successfully diagnose various visual dysfunctions, which validates the proposed approach.